PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2004/025247	04.08.2004	29.01.2004

International Patent Classification (IPC) or both national classification and IPC
C07K14/705, C12N15/12, A61K38/00, G01N33/50

Applicant
GENENTECH, INC.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:

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Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☒ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☒ furnished subsequently to this Authority for the purposes of search.

3. ☒ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. II Priority

1. ☐ The following document has not been furnished:

   ☐ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).

   ☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

   Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. ☒ The International Searching Authority has not been able to consider the validity of the priority claim because a copy of the earlier application whose priority has been claimed was not available to the International Searching Authority at the time that the search was conducted (Rule 17.1). This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

4. Additional observations, if necessary:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2004/025247

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 8-13, 15, 16-17 (partially), 20, 21, 22-35 (partially), 37, 39, 40 (partially), 42, 43-50 (partially); 41 and 43-50 (with respect to industrial application)

because:

☒ the said international application, or the said claims Nos. 41,43-50 relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the whole application or for said claims Nos. 8-13, 15, 16-17 (partially), 20, 21, 22-35 (partially), 37, 39, 40 (partially), 42, 43-50 (partially)

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:

   ☒ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ not paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1-7 (completely), 14 (completely), 16+17 (partially), 18+19 (completely), 22-35 (partially), 36 (completely), 38 (completely), 40 (partially), 41 (completely), 43-50 (partially)

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-50
	No:	Claims	none
Inventive step (IS)	Yes:	Claims	1-7,11,14,18-21,36,38,41,
	No:	Claims	8-10,12,13,15-17,22-35,37,39,40,42-50
Industrial applicability (IA)	Yes:	Claims	1-40
	No:	Claims	

2. Citations and explanations

   see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item III.

Claims 41-50 relate to *in vivo* methods of treatment and are considered by this authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item IV.

Lack of Unity of Invention

In the International Search Report (ISR) an objection to lack of unity was raised.

The separate inventions/groups of inventions are:

Invention 1: 1-7 (completely), 14 (completely), 16+17 (partially), 18+19 (completely), 22-35 (partially), 36 (completely), 38 (completely), 40 (partially), 41 (completely), 43-50 (partially)

Claims which relate to variants of the cysteine rich domain of BCMA wherein the ability to bind APRIL is retained or enhanced; nucleic acids encoding these variants; vectors and host cells comprising these nucleic acids; methods of using the variant polypeptides

Invention 2: 8-13 (completely), 15 (completely), 16+17 (partially), 20+21 (completely), 22-35 (partially), 37 (completely), 39 (completely), 40 (partially), 42 (completely), 43-50 (partially)

Claims which relate to variants of the cysteine rich domain of BCMA wherein the ability to bind BAFF is retained or enhanced; nucleic acids encoding these variants; vectors and host cells comprising these nucleic acids; methods of using the variant polypeptides

They are not so linked as to form a single general inventive concept (Rule 13.1 PCT) for

the following reasons:

Article 3(4)(iii) in combination with Rule 13.1 PCT stipulates that the international application shall relate to one invention only or to a group so linked as to form a single general inventive concept. Rule 13.2 PCT stipulates that where a group of inventions is claimed in one and the same international application, the requirement of unity of invention shall be fulfilled only when there is a technical relationship among those inventions involving one or more of the same or corresponding 'special technical features', i.e. technical features that define a novel and inventive contribution which each of the claimed inventions, considered as a whole, makes over the prior art.

The groups of inventions as set out above relate to variants of the cysteine rich domain of BCMA. The two groups do NOT share a common structural feature which is novel over the parent molecule, namely the CRD of BCMA itself. Moreover, the variants of the two groups have different functionalities. Variants belonging to the first group have retained or enhanced APRIL binding capacities, variants belonging to the second group have retained or enhanced BAFF binding capacities.

In response to the invitation to restrict or pay additional fees, the applicant has paid additional fees. The following examination report thus relates to both groups of inventions as set out above.

Re Item V.

1. Documents

The following documents are referred to in this communication:

D1: PATEL DARSHANA R ET AL: "Engineering an APRIL-specific B cell maturation antigen" JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 279, no. 16, 16 April 2004 (2004-04-16), pages 16727-16735, XP002318161 ISSN: 0021-9258

D2: BODMER J-L ET AL: "The molecular architecture of the TNF superfamily" TIBS TRENDS IN BIOCHEMICAL SCIENCES, ELSEVIER PUBLICATION, CAMBRIDGE, EN, vol. 27, no. 1, 1 January 2002 (2002-01-01), pages 19-26, XP004332356 ISSN: 0968-0004

D3: GORDON NATHANIEL C ET AL: "BAFF/BLyS receptor 3 comprises a minimal TNF receptor-like module that encodes a highly focused ligand-binding site." BIOCHEMISTRY, vol. 42, no. 20, 27 May 2003 (2003-05-27), pages 5977-5983, XP002318162 ISSN: 0006-2960

D4: MACKAY FABIENNE ET AL: "The TNF family members BAFF and APRIL: The growing complexity." CYTOKINE AND GROWTH FACTOR REVIEWS, vol. 14, no. 3-4, 2003, pages 311-324, XP002318163 ISSN: 1359-6101

D5: WO 01/60397 A (GENENTECH, INC) 23 August 2001 (2001-08-23)

D6: DATABASE UniProt 1 July 1993 (1993-07-01), "Tumor necrosis factor receptor superfamily member 17 (B-cell maturation antigen) BCMA" XP002328537 Database accession no. Q02223

D7: LIU YINGFANG ET AL: "Ligand-receptor binding revealed by the TNF family member TALL-1." NATURE (LONDON), vol. 423, no. 6935, 1 May 2003 (2003-05-01), pages 49-56, XP002328536 ISSN: 0028-0836

D8: OREN D A ET AL: "Structural basis of BlyS receptor recognition" NATURE STRUCTURAL BIOLOGY, NEW YORK, NY, US, vol. 9, no. 4, April 2002 (2002-04), pages 288-292, XP002286033 ISSN: 1072-8368

2. Subject-matter of the application

The present application relates to variants of the cysteine rich extracellular domain of the BCMA receptor (B-cell maturation antigen). TNF family members APRIL and BAFF both bind to the receptor via this domain. By shotgun alanine-scanning analysis, residues which are critical for APRIL and BAFF binding are identified. The application proposes variants with ligand specificity.

3. Novelty (Article 33(2) PCT)

The claimed subject-matter of both groups of inventions seems to be novel in the light of the cited prior art.

4. Inventive Step (Article 33(3) PCT)

The assessment of inventive step for protein variants depends on the technical effect that is associated with a particular variation. No inventive step can be acknowledged for a mutant protein that has essentially the same characteristics as the parent molecule (=non-functional modification). That means that BCMA variants which retain both APRIL **and** BAFF binding characteristics do not fulfil the requirements of Article 33(3) PCT.

4.1 Claim 17 relates to a BCMA polypeptide wherein one or more of the amino acids Q10, E12, Y13, F14, I22, Q25 and R27 have been altered. From the description and the figures (especially Figure 3), it seems that at least residues Q10 and E12 do not seem to be critical for binding of either APRIL or BAFF. A BCMA variant with mutations at this particular position would have no technical effect compared to the parent molecule (i.e. the wildtype BCMA molecule). Therefore, no inventive step can be acknowledged for the subject-matter of claim 17.

4.2 The remaining claims of **group 1 of inventions** all relate to BCMA variants wherein residue I22 has been altered to K. This leads to an altered ligand specificity of the BCMA molecule, namely the binding to APRIL is retained whereas the binding to BAFF is abolished.

Nothing in the prior art indicated that by substitution of I22 of BCMA, such altered ligand specificity could be achieved. The subject-matter of these claims is thus considered inventive.

4.3 The remaining claims of **group 2 of inventions** relate to BAFF binding BCMA variants. As pointed out above, inventive step for these variants can be acknowledged if the variation results in some technical effect (e.g. retained BAFF binding and abolished APRIL binding).

Except for the disclaimer, current claim 8 in its present wording has no structural limitations (every position of the general formula can be occupied by the wild type residue). Thus, claim 8 relates to **all** structural variants of BCMA which bind BAFF.

For the reasons pointed out above, no inventive step can be acknowledged for that subject-matter. The same is true for claims 9 and 10.

N.B: In addition, the residues crucial for binding of BCMA to BAFF have been disclosed in the prior art before (D7, page 52). Thus, it was quite obvious to the skilled person to retain these residues.

4.4 It must be further pointed out that the definitions given for positions x_6, x_{11}, x_{15}, x_{18} and x_{20} do not seem to be consistent with maintenance of BAFF binding. From the description (especially page 83) and Figure 3 it can be derived that:

- only conservative substitutions are accepted in position x_{11} (page 83, lines 18-19) with respect to BAFF binding.
- no substitution of x_{15} seems to be tolerated with respect to BAFF binding (page 83, lines 19-20, table 6, figure 3).
- an alanine substitution does not seem to be tolerated at position x_{18} (figure 3 and table 6)

4.5 Claim 11 relates to a BCMA variant wherein x_{20} is Y. Such a mutant retains its BAFF binding properties whereas the ability to bind APRIL is significantly reduced. Inventive step can be acknowledged for such a variant.
The same applies to claims 20 and 21.

4.6 Similar considerations as above apply to the sequences of claim 13. The fourth sequence corresponds to the Q25D mutation. No significant effect had been determined for that variant (Table 7 and page 86, lines 18-20) so that no inventive step can be acknowledged.

Re Item VIII.

5. Sufficiency of Disclosure (Article 5 PCT)

5.1 D1 teaches that residue Arg27 is required for high affinity binding of APRIL to BCMA.

The same can be deduced from Figure 3 of the application.
Thus, residue X_{20} of claim 1 should not be variable.

The same applies to residue X_{11} of claim 1. From Figure 3 of the application, it is apparent that substitution of this residue (leucine in the parent molecule) is not tolerated with respect to high affinity APRIL binding.

For the same reason, x_7 of claim 8 should not be variable.

5.2 In claims 1-5 and 8-11, the majority of the 34 amino acids representing the extracellular domain of BCMA are not defined. This authority is of the opinion that polypeptides with APRIL or BAFF binding properties are not sufficiently disclosed by these formulas for the following reason:

The skilled person is well aware that biological activities of proteins rely on correctly folded three-dimensional structures. Concerning BCMA, the prior art discloses that the cysteine-rich domain of BCMA has a saddle like architecture which sits on a horse-back like structure formed by its ligand (see D7). The saddle structure is thus indispensable for formation of the receptor-ligand interface.

The present application does not teach how to arrive at such a saddle structure starting from the general formula of claims 1 or claim 8. Only single or double mutations had been generated and investigated with respect to their binding behaviour. The application did not identify the residues which are crucial for correct folding of the BCMA, i.e. it has not been investigated how many and which amino acids of the wild type BCMA need to be retained.

Starting from the sequence of claims 1 or 8, the construction of APRIL/BAFF binding variants thus represents an undue burden for the skilled person. These claims do not fulfil the requirements of Article 5 PCT.

Similar arguments apply to dependent claims (2-6 and 9-12).